

REMARKS

Claims 22-24 and 28 are currently pending.

Applicants thank the Examiner for withdrawing the previous rejection of claims under 35 U.S.C. § 112, first and second paragraph and 35 U.S.C. § 102.

SPECIFICATION

The Examiner has objected to the previously amended title of the invention due to a typographical error. See Office Action at p. 2. Applicants have amended the title of the invention to correctly recite "mRNA."

CLAIM REJECTIONS

Rejection of claims under 35 U.S.C. § 103(a)

Collins and Van Der Mei

The Examiner has maintained the rejection of claims 22-24 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Publication No. 2002/0006432 to Collins ("Collins") in view of Van Der Mei, *J. Med. Microbiol.*, Vol. 49, p. 713-718 (2000) ("Van Der Mei"). See Office Action at p. 4. Claims 23-24 depend from independent claim 22.

Independent claim 22 relates to a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-1 mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420.

The Examiner states that "Collins teaches a method of treating a subject by administering bacteria of the genus *Bifidobacterium* to a subject (abstract)." See Office Action at p. 4. While the Examiner acknowledges that Collins "does not specifically teach the use of *Bifidobacterium* sp. 420 in the method of using the bacteria," the Examiner alleges that "[o]ne of ordinary skill in the art would have been motivated to use *Bifidobacterium* sp. 420 in the method of Collins because Collins teaches that any species of *Bifidobacterium* with probiotic effects may be used in the method, and further teaches methods for testing such strains for probiotic effects (p. 2, par. 14-15, p. 4, par. 81-83)." See Office Action at p. 7-8. Applicants respectfully traverse these statements.

MPEP 2145, paragraph X. A, states that “[a]ny judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in that art at the time the claimed invention was made and **does not include knowledge gleaned only from applicant’s disclosure**, such a reconstruction is proper” (emphasis added by Applicants) (citing *In re McLaughlin* 443 F.2d 1392, 1395 (CCPA 1971)).

When viewed as a whole, Collins relates to specific strains of *Bifidobacterium longum infantis* and, without hindsight, a person of ordinary skill in the art would not have considered the teachings of Collins to be applicable to all *Bifidobacterium* strains. For example, Collins at paragraph [0014] states that “[t]he invention provides a strain of *Bifidobacterium* isolated from resected and washed human gastrointestinal tract which is significantly immunomodulatory following oral consumption in humans.” (emphasis added). Reference to the bacterium in paragraphs [0015] to [0025] is to “**the**” strain – i.e. providing antecedence back to the singular “strain” referred to in paragraph [0014]. Additionally, paragraphs [0026] to [0029] actually specify the specific strain as *Bifidobacterium longum infantis* UCC35624. All of the Figures and Examples relate to *Bifidobacterium longum infantis*. Furthermore, paragraphs [0081] to [0083] relied on by the Examiner are part of Example 1 and relate to how the *Bifidobacterium longum infantis* strains used in the later Examples were isolated. Thus, a person of ordinary skill in the art reading Collins without the benefit of impermissible hindsight afforded by the claimed invention would consider Collins to relate to *Bifidobacterium longum infantis* strains only.

Further, Collins is a patent application and the absence of terminology explicitly relating to any *Bifidobacterium* species and the absence of a list in the description of other *Bifidobacterium* strains which the invention also relates to is further indicative of the intended narrow teaching to particular disclosed strains of *Bifidobacterium longum infantis*. Accordingly, a person of ordinary skill in the art would not have been motivated to combine Collins with any document which did not relate to a strain or strains of *Bifidobacterium longum infantis*.

For the avoidance of doubt, it can be seen that the present invention is not an extrapolation of the teachings of Collins. The present invention has for the first time demonstrated that *Bifidobacterium* sp. 420 increases COX-1 mRNA in a subject. This has not before been taught. Advantageously, this results in prevention of disease at an earlier stage before cytokine responses are induced. Therefore, conditions where alteration in epithelial cox function is believed to be an early key step in the pathogenesis (such as side effects associated

with nonsteroidal anti-inflammatory drugs) can be more efficiently inhibited by the present invention.

The Examiner however, further contends that “[r]egardless of whether Van Der Mei teaches the use of the probiotic *Bifidobacterium* species taught therein for a different purpose, one of ordinary skill in the art would have recognized that a *Bifidobacterium* species could have been selected for use from a finite number of members of the species, and would further have been motivated to select the species taught in the Van Der Mei reference because it had previously been used as a probiotic.” See Office Action at p. 9-10. The Examiner’s obviousness rejection again violates the basic considerations of obviousness as set forth in MPEP 2141 (“[t]he references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention.”).

Van Der Mei discloses the effects of probiotic bacteria on the prevalence of yeasts in oropharyngeal biofilms on silicone rubber voice prostheses. See abstract. This is a completely different field of use for the bacteria component compared to their effects on cytokine secretion by peripheral blood mononuclear cells described in Collins. There are no teachings either in Collins or in Van Der Mei which indicate that a bacteria which affects the prevalence of yeasts in oropharyngeal biofilms on silicone rubber voice prostheses would have effects on cytokine secretion by peripheral blood mononuclear cells as described in Collins. Thus, a person of ordinary skill in the art would have no motivation to combine the teachings of Collins and Van Der Mei.

Additionally, without hindsight reasoning, it would not be obvious for a skilled person starting from the teaching of Collins to look to a document such as Van Der Mei which does not disclose positive effects of a *Bifidobacterium* strain associated with the treatment of inflammatory disease and is actually silent with regard to inflammatory disease and does not link the specific *Bifidobacterium longum infantis* strains of Collins with other *Bifidobacteria*.

If a person of ordinary skill in the art were to try to extrapolate the teachings of Collins to other *Bifidobacterium* strains (which Applicants do not admit to be the case here), such a person would look to documents which teach probiotic bacteria which are capable of beneficially modifying and consequently alleviating observable symptoms in inflammatory disease because this is what Collins relates to. Therefore, the skilled person would look to documents disclosing the beneficial effects of other strains of *Bifidobacterium* associated with treatment of

inflammatory disease or at least to documents which link other *Bifidobacteria* and observations regarding inflammatory disease.

Van Der Mei is not even a review of different *Bifidobacteria* which may have probiotic effects. There is no indication in Van Der Mei that *Bifidobacterium* sp. 420 has advantages over any other strain of *Bifidobacterium*, let alone that it would be advantageous in the method of Collins. In fact, Van Der Mei finds *Bifidobacterium* sp. 420 not to be particularly effective, see abstract, which reads:

[e]xposure of oropharyngeal biofilms on voice prostheses to suspensions of *Bifidobacterium infantis* 420 or *Enterococcus faecium* 603 did not significantly reduce the number of yeasts in the biofilm. However, suspensions of *Lactobacillus fermentum* B54, *L. rhamnosus* 744 or *L. lactis cremoris* Sk11 led to a reduction in the number of yeasts harvested from voice prostheses.

Thus, it can be seen that Van Der Mei actually teaches away from using *Bifidobacterium infantis* 420. In view of the above, without the use of hindsight analysis, it can be seen that there is no motivation to use *Bifidobacterium* sp. 420 in the method of Collins.

The Examiner contends that “one of ordinary skill in the art would have recognized that a *Bifidobacterium* species could have been selected for use from a **finite** number of members of the species ...” (emphasis added). See Office Action at p. 9-10. Applicants respectfully traverse the Examiner's conclusion. This is an improper general allegation that has no support or documentary evidence that there are finite members of *Bifidobacterium* strains. At the time of the present invention there were a huge number of *Bifidobacterium* strains available. See for example, a partial list of *Bifidobacterium* strains attached at Appendix A. Of all of the strains available, there is nothing to motivate a person of ordinary skill in the art to select *Bifidobacterium* sp. 420 and substitute this strain in the method of Collins instead of the very specific strains of *Bifidobacterium longum infantis* taught by Collins.

In view of the above, in the absence of hindsight analysis, it can be seen that there is no motivation for a person of skill in the art to use *Bifidobacterium* sp. 420 in the method of Collins. Accordingly, Collins and Van Der Mei do not teach or suggest a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-1 mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420.

Since claims 23-24 depend from independent claim 22, those claims should be patentable

over the combination of Collins and Van Der Mei for at least the reasons described above. Applicants respectfully request reconsideration and the withdrawal of this rejection.

Collins, Van Der Mei, and Zimmer or Chen

The Examiner has rejected claims 22-24 and 28 under 35 U.S.C. § 103(a) as being unpatentable over Collins in view of Van Der Mei, and further in view of U.S. Patent No. 5,501,857 to Zimmer ("Zimmer") or U.S. Patent Publication No. 2001/0014322 to Chen et al. ("Chen"). Claims 23-24 and 28 depend from independent claim 22.

As explained in detail above, Collins and Van Der Mei do not teach or suggest a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-1 mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420.

Such defects are not remedied by Zimmer or Chen. Zimmer describes an "oral nutritional supplement, i.e., a dietary adjunct, for livestock which includes incompatible live microbial cultures, and vitamin and mineral supplements, each separated from the other via multiple encapsulation." See Abstract of Zimmer. In Example 10 of Zimmer, "[t]he microorganisms are a formulation of commercially available dormant *Bifidobacterium longum*." Zimmer does not teach or suggest a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-1 mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420.

Chen describes a microbe composition that includes "a symbiotic mixture of three lactic acid producing bacteria consisting of *Bifidobacterium bifidum* 6-1, *Lactobacillus acidophilus* YIT 2004 and *Streptococcus faecalis* YIT 0027." See paragraph [0025] of Chen. Chen does not teach or suggest a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-1 mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420. A person of skill in the art would not be motivated to combine Collins with Chen as Chen does not teach or suggest that *Bifidobacterium* sp. 420 increases the amount

of COX-1 mRNA in at least one cell of the subject.

None of the above-mentioned references, alone or in combination, teach or suggest teach or suggest a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-1 mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420.

Further, none of the cited documents teaches or suggests that a betaine compound (see claim 28) can be used in combination with *Bifidobacterium* in the methods of Collins, let alone that any *Bifidobacterium* strain can act in synergy with betaines in reducing intestinal inflammation. In contrast, the present invention has shown that *Bifidobacterium* sp. 420 can increase the level of COX-1 mRNA in a cell, can reduce intestinal inflammation caused by non-steroidal anti-inflammatory drugs in rats and can act in synergy with betaine for this purpose.


Since claims 23-24 and 28 depend from independent claim 22, those claims should be patentable over the combination of Collins, Van Der Mei and Zimmer or Chen for at least the reasons described above. Applicants respectfully request reconsideration and the withdrawal of this rejection.

CONCLUSION

Applicant believes that the claims are in condition for allowance. Should any fees be required by the present Reply, the Commissioner is hereby authorized to charge Deposit Account 19-4293.

Respectfully submitted,

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